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Original article

Effects of telemetric epicardial leads and ventricular catheters on arrhythmia incidence in cynomolgus monkeys

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ABSTRACT

Introduction: Utilization of implantable bio-telemetry devices represents a common approach to contemporary cardiovascular safety assessment. Depending on the specific needs of the study design, and corresponding surgical methodologies employed, application of telemetry devices may have more or less liability to interact with ongoing physiology. The potential for intrathoracic procedures (epicardial/intracardiac ECG lead arrangements, left ventricular catheterization) to influence baseline cardiovascular function, and particularly arrhythmia status is currently an important topic of consideration. **Methods:** Two experiments were performed to assess the post-surgical incidence of ventricular arrhythmias in cynomolgus monkeys instrumented with telemetry devices with 1) left ventricular pressure (LVP) transducers and epicardial lead array (N = 67), and 2) epicardial lead array without LVP catheter placement (N = 55). A third experiment (N = 18) was performed to prospectively, and definitively, investigate the effect of chronic left ventricular catheterization on the observed incidences of arrhythmias by means of multiple (pre- and post-surgery) electrocardiographic evaluations conducted on ~24 h of data per interval assessed up to ~12 months post-implantation. **Results:** The diversity and number of ventricular rhythm variants was considerably greater in animals instrumented with left ventricular catheters (62/67; 93%) compared to animals instrumented with epicardial leads only (21/55; 38.2%), and surgically naïve animals (9/18; 50%). Prior to surgery, the average frequency of all definitively characterized arrhythmias among experimentally naïve animals was 0.19/h; following surgical implantation of the telemetry device with epicardial leads and ventricular pressure catheter, the overall frequency of arrhythmia increased approximately 40-fold, to 7.19/h. **Discussion:** Similar to prior investigations in canines, the present results confirm an increased incidence in the rate and variety of ventricular arrhythmias in cynomolgus monkeys when instrumented with telemetry devices equipped with LVP catheters. Instrumentation with epicardial leads was not associated with an increase in arrhythmias above that expected as a function of normal biological variation in experimentally naïve animals of this species.

1. Introduction

Minimally invasive, implantable telemetry devices are routinely used in pre-clinical cardiovascular safety evaluation to access a variety of essential experimental endpoints such as arterial pressure, heart rate, and qualitative and quantitative aspects of the electrocardiogram (ECG). However, investigators are often interested in assessing indicators of myocardial performance in addition to basic hemodynamic and electrocardiographic parameters, which accordingly may require a catheter/transducer to be introduced and secured within the left ventricle to measure real-time variations in pressure from which appropriate functional endpoints may be derived (Hamlin & del Rio, 2010, 2012; Markert et al., 2007, 2009; Sarazan, Kroehle, & Main, 2011, 2012; Sarazan et al., 2011). The general surgical approach to catheter/transducer implantation produces damage, inflammation, and scarring within cardiac tissue, most notably in the vicinity of the ventricular apex, which is typically the selected route of catheterization (Henriques et al., 2010). Although the issue has not been amenable to definitive evaluation by the goals and selected methodologies of past basic research efforts (e.g., Sarazan et al., 2011, 2012), it is readily conceivable that myocardial damage, secondary to acute puncture injury through the ventricular apex and catheter placement, and/or due to the continued interaction of the catheter with adjacent transmural and endocardial tissues with potential associated foreign body response (Anderson, Rodriguez, & Chang, 2008; Baird, Bailie et al., 2013), could result in an enhanced susceptibility to ventricular arrhythmias. This seems particularly reasonable, given long-standing observations of

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increased arrhythmia expression in humans undergoing coronary catheterization procedures of a significantly less traumatic nature than chronic, trans-apical pressure catheter implantation (Fraser, Macaulay, & Rossall, 1962), and observations in monkeys of acute (up to ~72 h post-surgical) arrhythmia induction by, similarly less acutely traumatic, intracardiac lead placement (Yao et al., 2009).

While arrhythmias are accepted as potential sequelae of ventricular instrumentation, as conducted in contemporary preclinical safety studies, the presence of ventricular arrhythmias poses possible interpretative challenges with corresponding regulatory implications. The first challenge is to determine the definitive cause of arrhythmias observed on study as being either surgery-related, iatrogenic due to chronic catheterization, idiopathic, or drug-induced. The other challenge is to avoid inaccurate conclusions regarding causality given the heightened industry and regulatory concern regarding pharmacologically-induced alterations in cardiac electrophysiology and pro-arrhythmia in general. Recently, investigators have both acknowledged the validity of these concerns, and focused on potential approaches towards addressing the core issue(s). Enhanced technologies for long-term telemetric ECG monitoring, and perhaps more importantly, automated software to facilitate quantifying the frequency of arrhythmia expression in appropriately large samples of data (Koeppel, Labarre, & Zitoun, 2012), have become available. These technologies are beginning to be applied to research efforts aimed towards definitive characterization of baseline arrhythmia incidence rates by species (Chui, Derakhchan, & Vargas, 2012; Cools et al., 2011), and ultimately, elucidating the potential influence(s) of different telemetric implantation routines on arrhythmia expression (Baird, Bailie, et al., 2013), as has not been possible by application of alternative or historically-employed ECG recording techniques and protocols, even in very large samples (Gauvin, Tilley, Smith, & Baird, 2009).

A recent investigation in beagle dogs has confirmed an increase in the incidence and variety of ECG rhythm variants as a function of left ventricular catheterization to enable ventricular pressure telemetry. Cools et al. (2011) have described a substantial, time-dependent expression of increased arrhythmia incidence rates, which subsides in a temporally anterograde manner over the weeks to months following surgery. Based on these findings, the authors have recommended a minimum recovery period of ~8 weeks post-surgery, with appropriate arrhythmia screening methods, to identify animals acceptable for placement on any given cardiovascular safety study. Somewhat more limited investigations of this issue periodically have been conducted in the cynomolgus monkey (Holdsworth, O'Donohue, Dalton, & Baird, 2013; Holdsworth et al., 2010), an important species that is well-qualified for the purposes of cardiovascular safety evaluation (Ando et al., 2005; Baird, Dalton, & Gauvin, 2013; Baird, Gauvin, et al., 2013; Cavero, 2010; Hammond et al., 2001; Haushalter et al., 2008; Leishman et al., 2011; Lindgren et al., 2008; Sugiyama, 2008). However, there exists limited baseline data characterizing arrhythmia incidence in experimentally naïve cynomolgus monkeys (Chui et al., 2012; Macallum & Houston, 1993), and no relevant and/or definitive investigations into the potential for chronic, indwelling ventricular pressure catheters to alter baseline arrhythmia expression in this species. An equally compelling question is related to the potential influence of other intrathoracic variations in telemetry instrumentation (e.g., epicardial/pericardial lead placement) on arrhythmia expression in this species (Holdsworth, O'Donohue, Smith, & Baird, 2011) and others (Holdsworth et al., 2010).

The current investigations were initiated primarily to quantify the incidence of ventricular arrhythmias in cynomolgus monkeys instrumented with ventricular pressure catheters, and particularly those rhythm variants characterized as abnormal in either frequency or type. A secondary goal of these experiments was to assess, by comparison, the frequency of arrhythmias in cynomolgus monkeys instrumented only with intrathoracic (epicardial) lead arrays (i.e., no accompanying ventricular catheterization). Accordingly, two experiments were conducted to assess the incidence of ventricular arrhythmia in cynomolgus monkeys previously instrumented with telemetry devices with 1) left ventricular catheter placement and epicardial lead array (Experiment 1), or 2) epicardial lead array (Experiment 2). A final study (Experiment 3) was performed to prospectively, and definitively, investigate the effect of chronic left ventricular catheterization on observed incidences of ventricular and overall arrhythmia by means of multiple (pre- and post-surgery) electrocardiographic evaluations conducted on ~24 h of data per interval assessed for up to ~12 months post-implantation.

2. Methods

2.1. Test system

All procedures were conducted in compliance with the Animal Welfare Act and the Guide for the Care and Use of Laboratory Animals within an AAALAC-accredited test facility. Animals were received from USDA-approved laboratory animal vendors previously audited (including requisite site inspections, as required) by staff veterinarian members of the MPI Research IACUC. Male and female cynomolgus monkeys (*Macaca fascicularis*; N = 140) of predominantly Chinese origin were received from Covance Research Products and Charles River Laboratories. Numbers of male and female animals allocated to each of three experiments are indicated in Table 1. A subset of the animals (26/67) included in Experiment 1 were from Mauritius. At 3 to 4 years of age, available animals were selected from an MPI Research Stock Telemetry Colony and qualified for study based on pre-study veterinary physical examinations, strip chart electrocardiograms, and clinical pathology assessments. Animals were allowed to acclimate to the general features of the telemetry recording environment for at least 4 weeks prior to the initiation of any study-specific procedures.

Table 1
Surgical procedures conducted in Experiments 1–3.

Experiment	N (M/F)	Surgical procedure	Telemetry device
1[a]	67 (33/34)	Left ventricular catheterization/epicardial (base-apex) ECG lead	(D70-PCTP)
2[b]	55 (35/20)	Epicardial (base-apex) ECG lead only	(D70-PCT)
3[c]	18 (10/8)	Left ventricular catheterization/epicardial (base-apex) ECG lead	(D70-PCTP)

[a,b]These animals were drawn as available from the testing facility telemetry stock colony over the course of approximately 12 months, and assessed for arrhythmia status 32 ± 4 days from the time of surgical implantation (Mean ± SEM).
[c]These animals were ordered experimentally naïve and assessed for arrhythmia prior to surgery and at between 5 and 8 additional intervals over the course of the next 12 months post-surgery (average number of days post-surgery prior to initial arrhythmia determination = 20 ± 0.9 days).
M — male.
F — female.